## REMARKS

Claims 13, 15-21, 23, 25-33, 35-37, 39, 45, 46, 50, 52-62, 65-67, 69-71, and 73-119 constitute the pending claims in the present application. The Examiner has indicated that claims 25-27, 34-37, 52, and 55, 56, 62, 65-67, 69-71, 73-75, 79-84, 86, and 113-115 are withdrawn from consideration as allegedly directed to a nonelected invention. Applicants maintain, however, that these claims are properly dependent on elected independent claims and should be considered together upon determining that such independent claims are allowable, pursuant to MPEP 809.02(c). For example, claims 35-37 are dependent on claims 13 and 15-20. Applicants submit that once claims 13 and 15-20 are found allowable, dependent claims 35-37 should be allowable as well. Applicants respectfully request reconsideration and rejoinder of claims that depend from independent claims currently being examined.

In order to expedite prosecution of the instant application, claims 13, 21, 23, 33, 45, 87, 90, 91, 92, 93, and 94 are being amended to more particularly describe the claimed invention. Amendments include reference to impaired islet function, reference to a PYY agonist having an amino acid sequence whose corresponding nucleic acid sequence, ascertainable by one of skill in the art, is able to hybridize to SEQ ID NO:1, reference to the amount of PYY or PYY variants, and/or correction of typographical errors. Applicants amend without prejudice, reserving the right to prosecute claims of identical scope to the unamended claims. Amendments to claims 28, 88, 89, 102, 106-112, and 116-119 more particularly describe the claimed invention. Claims 95 and 99 are cancelled without prejudice. New claims 120-123 are added. Support for new claims 120 and 123 drawn to a composition that includes GLP-1 can be found at least at page 28, lines 14-16, of the specification and originally filed claims 30 and 31. Support for new claims 121 and 123 drawn to nasal administration can be found at least at page 35, lines 36-37, of the specification. Support for new claims 122 and 123 drawn to PYY(3-36) can be found at least at page 10, lines 27-28, of the specification. Applicants submit that no new matter is introduced by the instant amendments.

Applicants thank the Examiner and her Supervisor for courtesies extended during an interview conducted December 2, 2004. In compliance with 37 CFR §1.33(b), Applicants submit that, as set forth in the Interview Summary,

1) no exhibit was shown nor any demonstration conducted;

2) all pending claims (claims 13, 15-21, 23, 25-33, 35-37, 39, 45, 46, 50, 52-62, 65-67, 69-71, and 73-119) were discussed;
3) references Bottcher *et al.* Pancreas 4(3):282-8, 1989 and Bertrand *et al.* Pancreas 7(5):595-600, 1992 were discussed;
4) the principal proposed amendments of a substantive nature are described in the Interview Summary;
5) the general nature of the arguments presented to the Examiner is that the invention described in the pending claims are enabled by the specification and that the references cited by the Examiner do not render the present invention non-enabled as the references are not directed to the same subject matter as the invention. Moreover, the examples in the present application and the *in vivo* diabetic rat data enable the therapeutic claims;
6) the scope of the claims alleged to be duplicative were discussed; and
7) the general results are described in the Interview Summary.

Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the prior Office Action.

1. Applicants note that the finality of the previous rejection has been withdrawn pursuant to 37 CFR 1.114. Applicants additionally note that the amendments filed 24 March 2004 have been entered in full.

2. Applicants note with appreciation that the Information Disclosure Statement filed 24 March 2004 has been received, considered, and placed in the file of the present application.

3. Claims 13, 15-21, 23, 28-33, 39, 45, 45, 50, 53, 54, 57-61, 76-78, 85, 87-112, and 116-119 are rejected under 35 U.S.C. 112, first paragraph, for allegedly failing to enable one of skill in the art to practice the claimed invention. Applicants traverse this rejection and contend that the rejection is moot in light of the amended claims.

The basis of this rejection is two fold. First, the teachings of two prior art references (Bottcher et al. and Bertrand et al.) allegedly undermine the enablement of the presently claimed methods. Specifically, Applicants' claims directed to methods of using PYY and functional

variants of PYY to, for example, increase glucose-responsiveness of pancreatic islets and cells allegedly lack enablement because Bottcher et al. and Bertrand et al. suggest that PYY inhibits insulin secretion.

Applicants respectfully disagree with the Patent Office. While not acceding to conclusions reached by the authors, as explained in the interview, neither the teachings of Bottcher et al. nor Bertrand et al. are inconsistent with Applicants' disclosure. For example, Applicants' examples show that PYY increased glucose-stimulated insulin release in cells that would otherwise lose this ability (see *e.g.*, 1st instance of "Example 5" and Fig. 4) or cells that do not have this ability at all. In contrast, the experiments of Bertrand et al. only look at islets under conditions where glucose responsiveness is still retained by the islets, for example the islets are used "immediately after isolation" (page 596, last sentence carried over to page 597). Accordingly, unlike the controls (no PYY administration) of the instant application that lose glucose responsiveness, those in the Bertrand experiments maintain their glucose responsiveness. Similarly, Bottchard et al. describe the effect of PYY on female mice of the NMRI strain. The mice are apparently healthy mice, with normal glucose responsive cells (for example, see controls). Because neither Bottchard et al. nor Bertrand et al. explore the effect of PYY on cells that would lose glucose responsiveness, cells that do not possess glucose responsiveness, or animals with altered glucose metabolism, these references do not disclose information that is contrary to what is disclosed in the instant application. Therefore, Applicants submit that these references fail to undermine the enablement of the claimed invention.

Further, Applicants maintain that Applicants' working examples showing that PYY increases pancreatic function (e.g., glucose-responsiveness) support claims directed to the use of some penumbra of PYY variants. As outlined in detail in Applicants' previous responses, the specification provides a detailed description of methods of making and testing variants using combinatorial mutagenesis (page 22, line 24-page 23, line 17). Furthermore, the specification provides mouse models in which PYY variants can be tested for efficacy in the subject methods. Given the extensive guidance provided in the specification, as well as the high level of skill in the art, Applicants contend that one of skill in the art can readily make and test PYY variants to identify variants which meet the structural and functional limitations recited in the claims without undue experimentation.

Furthermore, Applicants have amended the claims to provide additional functional limitations to describe the claimed subject matter. The extensive structural and functional description of the claimed subject matter readily permits one of skill in the art to envision the claimed subject matter, and furthermore to make and use the claimed subject matter. In light of the extensive guidance provided by the specification, the high level of skill in the art at the time of filing, and the structural and functional guidance provided by the specification, Applicants contend that the claims are enabled throughout their scope.

Additionally however, Applicants do not merely rely upon the ability of one of skill in the art to make and test peptide variants in order to select variants for use in the methods of the present invention. Applicants reiterate the arguments of record, and remind the Examiner that several PYY variants have been identified and the ability of these variants to mimic one or more functions of PYY has been demonstrated. Accordingly, these examples demonstrate that not only **could** one of skill in the art make and test variants to identify those variants with particular functional attributes, but one of skill in the art **did** make and test variants to identify variants with particular attributes.

Applicants contend that in light of the teachings of the specification, the structural and functional language recited in the claims, and the high level of skill in the art, Applicants' claims are enabled throughout their scope. Reconsideration and withdrawal of this rejection is respectfully requested.

The second ground for rejection is that the specification allegedly fails to enable claims directed to methods of treating a disease in an animal, as it is alleged that the physiological response of cells in culture does not necessarily or predictably correlate with an effect *in vivo*. Applicants traverse this rejection to the extent that it is maintained in light of the amended claims.

A similar rejection was raised by the Patent Office on page 8 of the March 12, 2001 and page 10 of the August 27, 2001 Office Actions. These rejections were overcome by Applicants response filed January 28, 2002. A copy of the appropriate pages and exhibits of the response are attached. In brief, Applicants provide ample evidence of *in vitro* functions of PYY showing a strong correlation to *in vivo* results. Applicants submit that these data are sufficient for one of

ordinary skill in the art to reasonably believe that the PYY results *in vitro* would be predictive of results *in vivo*. As support for the predictive nature of the *in vitro* data, Applicants provide *in vivo* data of PYY's ability to control glucose levels in rats predisposed to diabetes. Accordingly, Applicants' claims are enabled throughout their scope, and reconsideration and withdrawal of this rejection is requested.

Claims 95 and 99 are rejected because it is alleged that the specification fails to teach that exocrine or endocrine cells can be glucose responsive. Solely to advance prosecution of the instant claims, Applicants have cancelled these claims reserving the right to prosecute claims of identical or similar scope in a later application.

4. Claims 13, 90, 92, and 93 are objected to for allegedly being of indistinguishable scope. Applicants traverse this objection and respectfully point out that the scope of claims 13 and 93 and claims 90 and 92 is different.

Claim 13 is directed to "[a] method for *inducing or enhancing* the glucose-responsiveness of a pancreatic islet or pancreatic cell" while claim 93 is directed to "[a] method for *maintaining* glucose-responsiveness of a pancreatic islet or pancreatic cells." Applicants contend that the plain meaning of "inducing or enhancing" versus "maintaining" indicates that claims 13 and 93 are of differing scope.

Claim 90 is directed to "[a] method for *maintaining or restoring* a function of pancreatic *β cells*" while claim 92 is directed to "[a] method for *maintaining* glucose-responsiveness of a pancreatic islet or pancreatic cells." Applicants contend that claims 90 and 92 differ with respect to both the target cell type (β cells versus pancreatic islets or pancreatic cells) and with respect to the effect of PYY (maintaining or restoring versus maintaining). Accordingly, Applicants contend that claims 90 and 92 are of differing scope.

## CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Should an extension of time be required, Applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this submission be charged to **Deposit Account No. 18-1945, under Order No. CIBT-P01-058.**

Respectfully Submitted,

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Melissa S. Rones Reg. No. 46,862

Melissa S. Rones
Reg. No. 54,408

***Customer No: 28120***
Docketing Specialist
Ropes & Gray
One International Place
Boston, MA 02110
Phone: 617-951-7000
Fax: 617-951-7050